Benzotrichloride; CASRN 98-07-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Benzotrichloride

File First On-Line 07/01/1990

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<th>Last Revised</th>
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*A comprehensive review of toxicological studies was completed (July 13, 2006) - please see section II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Benzotrichloride
CASRN — 98-07-7

Not available at this time.
I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Benzotrichloride  
CASRN — 98-07-7  

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Benzotrichloride  
CASRN — 98-07-7  
Last Revised — 07/01/1990

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Based on inadequate human data and sufficient evidence of carcinogenicity in animals; namely, significantly increased incidences of benign and malignant tumors at multiple sites in one strain of female mice treated orally, dermally, and by inhalation. There is also evidence of mutagenicity in a variety of test systems.
II.A.2. Human Carcinogenicity Data

Inadequate. Studies have shown that occupational exposure to the process of benzoic chloride production process, which involves benzoic trichloride as a major reaction intermediate, may increase the risk of cancer-induced mortality. The available human data for benzoic trichloride alone are considered inadequate because the studies included small numbers of cancer deaths and were based on exposure to mixtures of chlorinated compounds. In addition, data on cigarette smoking were incomplete.

Sakabe et al. (1976) reported three cancer deaths among 41 workers employed in a benzoic chloride production plant in Japan between 1954 and 1972. Two of the deaths were from lung cancer, both in smokers in their forties. The third cancer death was from maxillary malignant lymphoma in a 50-year-old worker not specified as a smoker or nonsmoker. A fourth case of cancer diagnosed as squamous cell carcinoma of the lung was identified in a nonsmoking worker still living at the time the analysis was undertaken in 1973. The number of years these four workers were employed in benzoic chloride production ranged from 6 to 15 years. The number of deaths from lung cancer (2) was significantly higher than the number expected (0.06), based on the Japanese national rates for death from lung cancer in males. In addition to benzoic trichloride and benzoic chloride, these workers were exposed to toluene, chlorine gas, hydrogen chloride, benzyl chloride, benzal chloride, other chlorinated toluenes and polymerized products from the process. However, the authors considered it highly possible that the four cancer cases were produced by exposure to benzoic trichloride or benzoic chloride since these are the major products of the two chemical reactions in the production process. In addition, it was noted that these two chemicals have generally been used as synthetic reagents because of their high chemical reactivity. In a subsequent report, two lung cancer deaths were identified among workers engaged in benzoic peroxide and benzoic chloride production at another plant, in which the total number of workers ranged from 13 in 1952 to 40 in 1963 (Sakabe and Fukuda, 1977). The two individuals, one of whom was a smoker, were in their forties and had worked in benzoic chloride production for 6 to 18 years. The number of deaths expected among these workers was not reported.

Sorahan et al. (1983) conducted a study of cancer mortality among 953 workers at a British factory engaged in production of chlorinated toluenes. As in the Japanese plants, there was exposure to toluene (the starting material), benzoic trichloride and benzoic chloride (the major reaction products), as well as benzyl chloride, benzal chloride and other materials. The cohort of exposed workers consisted of 163 males employed for at least six months between 1961 and 1970. Some of these individuals started employment as early as 1923. Of the 10 deaths from cancer (25 total deaths) reported in this group, 5 were due to digestive system cancers and 5 to respiratory cancers, compared with 1.24 and 1.78 expected, respectively. The standardized mortality ratio for each of these sites was significantly higher than expected, based on mortality
rates for England and Wales. A survival analysis using the Cox Proportional Hazards model, adjusting for age at entry to the survey and the time period when employment began, was also conducted. This analysis showed a statistically significant association between estimated cumulative exposure and deaths from cancer at all sites (but neither digestive nor respiratory cancers individually), for persons first employed before 1951. The association was not significant for all entry cohorts combined. Interpretation of this study is limited by several factors, including possible bias in assignment of exposure categories, exposure to multiple compounds and lack of data on smoking.

Another retrospective mortality study reported on a cohort of 697 male workers who were exposed to benzyl chloride, benzotrichloride and benzoyl chloride at a chlorination plant (Wong and Morgan, 1984). The length of employment at the plant ranged from 1 year to >35 years. Seven deaths from respiratory cancer were found in the total cohort compared with 2.84 expected deaths based on U.S. mortality rates for males. Five of these deaths occurred in workers employed for at least 15 years. This was significantly greater than the 1.32 deaths expected for this subgroup. The results of this study were confounded by multiple exposures and lack of data on smoking.

In summary, because of small sample sizes, lack of data on cigarette smoking and the fact that exposure was to a mixture of halogenated intermediates, the available human data are insufficient to determine the potential carcinogenicity of benzotrichloride exposure.

II.A.3. Animal Carcinogenicity Data

Sufficient. The animal data consist of oral, inhalation and skin painting studies in female mice of a single strain.

Groups of 40 nine-week-old female ICR mice were gavaged with 0.043, 0.17, 0.7, or 2.7 mg benzotrichloride of unknown purity in 0.1 mL sesame oil twice weekly for 25 weeks (Fukuda et al., 1978). The 40 control animals were untreated. Surviving animals were killed and examined histologically 18 months after the start of treatment. Mortality was significantly increased in the two highest dose groups, reaching 50% at 6.5 months in the highest dose group and at 16.5 months in the second highest dose group. Forestomach squamous cell carcinoma was observed in 0/35, 0/37, 2/38, 22/40, and 24/35 animals in the control to high-dose groups, respectively. The incidence was significantly increased at the two highest dose levels. Lung adenocarcinoma was reported in 0/35, 1/37, 9/38, 16/40, and 10/35 animals; the incidences were significantly increased in the three highest dose groups. Lung adenoma was observed in approximately equal proportions to carcinoma (1/35, 0/37, 6/38 17/40, and 10/35; significantly increased at the two highest dose levels). Thymoma incidence (0/35, 0/37, 1/38, 2/40, and 7/35) was significantly increased only at the highest dose.
Yoshimura et al. (1979, 1986) exposed 37 5-week-old female ICR-JCL mice to an average concentration of 1.6 ppm (12.8 mg/cu.m) benzotrichloride of unknown purity vaporized at room temperature, twice weekly for 30 minutes for 12 months. Surviving animals were observed for an additional 0 to 3 months. Thirty control animals were maintained for 12 months only. In the 10 treated mice that died before 12 months, the following tumor incidences were observed: 7 lung adenomas, 1 lung adenocarcinoma, and 1 skin papilloma. Ten treated mice were sacrificed at 12 months; lung adenoma was found in 5, adenocarcinoma in 4, skin papilloma in 3 and skin carcinoma in 1. Lung adenoma was observed in 3/30 of the control animals that died or were killed at 12 months. Of 8 treated mice that died from 12 to 15 months, 3 had lung adenoma, and 3 adenocarcinoma. None had skin tumors. The remaining 9 mice were killed at 15 months; 2 had lung adenomas, 5 had adenocarcinomas, 2 had skin papillomas, and 3 had skin carcinomas. Thus, the proportion of malignant tumors at these sites increased with time. During the first 12 months, 3 malignant lymphomas were observed, and 1 was observed between 12 and 15 months. The overall incidence of tumors was 30/37 (81%) for the lung (compared to 3/30 in controls), 10/37 (27%) for the skin (0/30 in controls), and 4/37 (11%) for malignant lymphoma (0/30 in controls). The incidence at each of these sites was significantly elevated compared to the control incidence. Yoshimura et al. (1979) noted that all treated animals had severe bronchitis and bronchial pneumonia.

In a related study, 32 5-week-old female ICR mice were exposed by inhalation to an average concentration of 6.8 ppm (54.8 mg/cu.m) benzotrichloride of unknown purity, vaporized at 50°C (Takemoto et al., 1978; Yoshimura et al., 1986). The animals were exposed twice weekly for 30 minutes for 5 months, followed by a 1- to 5-month observation period. The control group of 30 animals was observed for 12 months; no results were reported. Of 12 treated mice that died during the exposure period, 2 had lung adenomas; 6 had malignant lymphoma. At the end of the treatment, 6/11 mice had developed lung adenomas and 1/11 had squamous-cell carcinoma of the skin. After 10 months, 8/9 had lung adenomas, 1/9 had lung adenocarcinoma, 3/9 had skin carcinoma, 4/9 had skin papillomas, and 2/9 had malignant lymphoma. The overall tumor incidence was 17/32 (53%) for the lung, 8/32 (25%) for the skin, and 8/32 (25%) for malignant lymphoma, compared with 3/30 lung adenomas and no other tumors in the controls. Benzoyl chloride administered under the same conditions to 7 mice induced 2 skin papillomas by 10 months, and 3 lung tumors (1 adenoma, 2 carcinomas) by 14 months.

Fukuda et al. (1981) conducted a series of three skin-painting studies on specific pathogen-free ICR mice, using benzotrichloride (reagent grade) at successively smaller doses for longer periods. The compound was administered undiluted or dissolved in benzene. The animals were housed at about 10 per cage. In the first experiment, three groups of 19 to 22 14-week-old female ICR mice received skin applications of 25 uL benzene (vehicle control), 25 uL benzotrichloride (34.3 mg), or 25 uL of a 50% solution of benzotrichloride (17.1 mg) in benzene. The doses were given twice weekly for 3 weeks, then once weekly until the mice were killed at 7.2 months.
Assuming a total of 34 doses, the high dose corresponded to a total of approximately 1165 mg (average dose rate of 5.4 mg/day) and the low dose to 582.4 mg (average dose rate of 2.7 mg/day). Mortality at the termination of the experiment was 0, 10, and 46% in the control, low- and high-dose groups, respectively. The number of mice with tumors was 0/20, 17/19, and 21/22 in the control, low-dose, and high-dose groups, respectively. The reported incidence of tumors at specific sites for low- and high-dose groups was 6/19 and 12/22 for skin carcinomas, 10/19 and 9/22 for lung adenoma/carcinoma, and 1/19 and 6/22 for thymus lymphoma.

Similar results were obtained in the second experiment in which three groups of 9 to 10 3-week-old female ICR mice received dermal application of 10 uL of benzene (vehicle control), 10 uL benzotrichloride or 10 uL of a 50% benzotrichloride:benzene solution 3 times/week for 4 weeks then twice weekly thereafter until sacrifice at 9.8 months. The mice in the high-dose group were sacrificed at 5.7 months because of high mortality and morbidity. The high dose thus represented a total of 740 mg and the low dose 603 mg (4.3 and 2.1 mg/day, respectively). Mortality at termination was 0, 60, and 80% for the control, low-dose, and high-dose groups, respectively. The number of mice with tumors was 0/10, 10/10, and 8/9 in the control, low-dose, and high-dose groups, respectively. Reported tumor incidences at specific sites for the low- and high-dose groups was 7/10 and 4/9 for skin carcinomas, 10/10 and 3/9 for lung adenoma/adenocarcinoma, and 3/10 and 5/9 for thymus lymphoma. In addition, two squamous-cell carcinomas of the lips and one squamous-cell carcinoma of the forestomach were reported in the low-dose mice. These tumors were assumed to result from the ingestion of benzotrichloride caused by licking of the skin.

In the third experiment, 2 groups of 20 7-week-old female ICR mice received skin applications of 25 uL benzene (controls) or 25 uL of a 9.2% solution of benzotrichloride in benzene twice weekly for 11.7 months. The total dose was approximately 315 mg (0.9 mg/day). Surviving mice were sacrificed at 18.7 months (controls) or at 13.3 months (benzotrichloride- treated). Mortality at termination was 20% in the controls compared with 35% in the treated group. In the control group, 2/20 mice had lung adenomas while in the treated group, 13/19 had skin carcinoma and 11/19 had lung adenoma/carcinoma. Nineteen other tumors, attributed to licking, were observed in the lips, tongue, esophagus, forestomach and glandular stomach of the treated mice.

Stoner et al. (1986) administered benzotrichloride (at least 99% purity) in tricaprylin to both sexes of A/J mice (11 to 15/group) by intraperitoneal injection at doses of 12, 30, or 60 mg/kg, 3 times/week for 8 weeks. Total doses were 287, 719, or 1440 mg/kg. The mice were observed for 16 weeks following the exposure period. Lung adenomas were observed in 4/15 vehicle- treated controls of each sex, while 100% of the animals in all treated groups developed lung adenomas. The tumor incidence was significantly increased in each group compared with controls, and there was a significant dose-related trend in the average number of tumors per mouse. In other organs, only tumors observed as gross lesions at necropsy were further examined. In the highest dose
group, three lymphomas and two kidney sarcomas, which reportedly occur rarely in this strain, were observed.

II.A.4. Supporting Data for Carcinogenicity

Results of mutagenicity testing of benzotrichloride in bacterial systems are equivocal. Positive results were obtained in a rec assay in Bacillus subtilis and in reverse mutation assays in Escherichia coli and Salmonella typhimurium when a metabolic activation system was present (Yasuo et al., 1978). In another study, negative results were found for reverse mutation in S. typhimurium and for forward mutation in Saccharomyces cerevisiae in the absence and presence of metabolic activation (Jagannath, 1978). Koshi and Fukuda (1986) reported slight increases in chromosomal aberrations in bone marrow cells of rats exposed to 1 ppm benzotrichloride for 6 hours/day, 5 days/week, during 1-, 3- and 6-month periods. A significantly increased frequency of sister chromatid exchanges in peripheral lymphocytes was also observed.

The predominant metabolite of benzotrichloride in the rat is benzoic acid, which is excreted in the urine (greater than 90%) following conjugation with glycine and formation of hippuric acid (Yu and Nietschmann, 1980). Benzoic acid has been tested for mutagenicity and results have been consistently and unequivocally negative (U.S. EPA, 1987).

Benzyl chloride and benzal chloride, which are also intermediates in the benzoyl chloride production process, are structural analogues of benzotrichloride and have been shown to be carcinogenic in animals (Preussmann, 1968; Fukuda et al., 1981). (Benzyl chloride is classified as B2.) Both of these compounds have also demonstrated mutagenic activity (Yasuo et al., 1978; Rosenkranz and Poirier, 1979).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Slope Factor for use with Dietary Intakes — 1.3E+1 per (mg/kg)/day

Drinking Water Unit Risk — 3.6E-4/ug/L

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:
Risk Level | Concentration
---|---
E-4 (1 in 10,000) | 3E-1 ug/L
E-5 (1 in 100,000) | 3E-2 ug/L
E-6 (1 in 1,000,000) | 3E-3 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — lung, adenocarcinoma  
Test animals — mouse/ICR, female  
Route — gavage, sesame oil  
Reference — Fukuda et al., 1978

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II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

No model fit adequately using all five doses; therefore, the high dose was dropped in deriving the slope factor.
Transformed animal doses were calculated by dividing the experimental dose by the reference mouse body weight of 0.03 kg and by multiplying by 2 days/7 days and by 25 weeks (length of treatment)/78 weeks (length of experiment). The human equivalent doses were calculated by multiplying the animal doses by the cube root of the ratio of the mouse body weight to the reference human body weight (70 kg). Since the length of the experiment in mice was less than the lifespan of mice, the doses were further corrected by the cube of 78 (length of experiment)/104 (lifespan of animal).

Using the data from Fukuda et al. (1978), slope factors were derived for the incidence of forestomach squamous-cell carcinoma (6.0 per (mg/kg)/day) and thymoma (1.4 per (mg/kg)/day) in female mice. Since the slope factor derived from the data on adenocarcinomas of the lungs is higher than that generated from the data on tumors in the forestomach and thymus, it was recommended as the risk estimate. (Because individual pathology data were not presented, the tumors could not be pooled across sites to derive the risk estimate.)

The slope factor for benzotrichloride is approximately 2 orders of magnitude greater than that for benzyl chloride (1.7E-1 per (mg/kg)/day), a structurally similar and process-related chemical.

The unit risk should not be used if the water concentration exceeds 3E+1 ug/L, since above this concentration the slope factor may differ from that stated.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

A sufficient number of animals was used for analysis of late-developing tumors. Benzotrichloride was administered by a relevant route of exposure at several doses for a significant portion of the animals' lifespan. Histological examination was comprehensive. There is uncertainty associated with adjusting for an experimental dose administered for a relatively short exposure duration over the lifetime of the animal. The uncertainty relates both to the method by which risk estimation is carried out and the mechanism by which the agent may cause cancer.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)
II.D.1. EPA Documentation


The 1986 Health and Environmental Effects Profile for Benzotrichloride has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 04/05/1989, 05/03/1989, 05/30/1989, 08/02/1989

Verification Date — 08/02/1989

A comprehensive review of toxicological studies published through July 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for Benzotrichloride and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Benzotrichloride
CASRN — 98-07-7

VI.A. Oral RfD References

None
VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References


## VII. Revision History

Substance Name — Benzotrichloride  
CASRN — 98-07-7

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## VIII. Synonyms

Substance Name — Benzotrichloride  
CASRN — 98-07-7  
Last Revised — 07/01/1990

- 98-07-7  
- AI3-02583  
- BENZENE, (TRICHLOROMETHYL)-  
- BENZENYL CHLORIDE  
- BENZENYL TRICHLORIDE  
- BENOZOIC TRICHLORIDE  
- BENZOTRICHLORIDE  
- BENZOTRICLORURO [SPANISH]  
- BENZYLIDYNE CHLORIDE  
- BENZYL TRICHLORIDE  
- CHLORURE DE BENZENYLE [FRENCH]  
- CHLORURE DE BENZYLIDYNE [FRENCH]  
- HSDB 2076  
- OMEGA,OMEGA,OMEGA-TRICHLOROTOLUENE  
- PHENYL CHLOROFORM
- PHENYLCHLOROFORM
- PHENYLTRICHLOROMETHANE
- RCRA WASTE NUMBER U023
- TOLUENE TRICHLORIDE
- TOLUENE, ALPHA, ALPHA, ALPHA-TRICHLORO-
- TRICHLOROMETHYLBENZEEEN (DUTCH)
- TRICHLORMETHYLBENZOL (GERMAN)
- TRICHLOROMETHYLBENZENE
- (TRICHLOROMETHYL)BENZENE
- 1-(TRICHLOROMETHYL)BENZENE
- TRICHLOROPHENYL METHANE
- ALPHA, ALPHA, ALPHA-TRICHLOROTOLUENE
- TRICLOROMETILBENZENE (ITALIAN)
- TRICLOROTOLUENE (ITALIAN)
- UN 2226